IN THE NAME OF GOD

دانشگاه علوم پزشکی و خدمات بهداشتی ـ درمانی
استان قزوین

Relation between apoptosis and microorganisms

Superviser:Dr.Aslanimehr
Presented by :Mehri Sadeghi

What is it?

Why is it important?

How is it controlled?

What is its role in age-related disease?

Forms of cell death

"Classic"

Necrosis	Apoptosis	Mitotic catastrophe
Passive	Active	Passive
Pathological	Physiological or pathological	Pathological
Swelling, lysis	Condensation, cross-linking	Swelling, lysis
Dissipates	Phagocytosed	Dissipates
Inflammation	No inflammation	Inflammation
Externally induced	Internally or externally induced	Internally induced

- **Cell death by injury**
  - -Mechanical damage
  - -Exposure to toxic chemicals
- **Cell death by suicide**
  - -Internal signals
  - -External signals

Apoptosis

- Apoptosis or programmed cell death, is carefully coordinated collapse of cell, protein degradation , DNA fragmentation followed by rapid engulfment of corpses by neighbouring cells. (Tommi, 2002)

- Essential part of life for every multicellular organism from worms to humans. (Faddy *et al.*,1992)

Apoptosis

- Apoptosis is the primary means for eliminating unwanted cells in multicellular organisms in order to preserve tissue homeostasis and function. It is characterized by distinct changes in the morphology of the dying cell that are orchestrated by a series of discrete biochemical events.

Relation between apoptosis and microorganisms

- Several pathogenic or opportunistic bacteria can induce or inhibit host cell apoptosis.
- The modulation of cellular pathways that results in the induction or delay of host cell apoptosis is an important mechanism of bacterial virulence.
- These processes can be mediated by various host cell signaling pathways that are subverted by the bacteria.

Relation between apoptosis and microorganisms

Pathogens can activate apoptotic proteins such as caspases,
inactivate anti-apoptotic
proteins such as NFB and mitogen-activated protein kinases, or up-regulate the endogenous receptor/ligand.

- system that induces apoptosis, generally when the bacteria are bound to the host cell surface.

- The bacteria that use apoptotic mechanisms include a variety of facultative intracellular pathogens

- Bacteria induced

apoptotic or anti-apoptotic processes are often related to the ability of the bacteria to reach the host tissues

Some situations of cell death in unicellular eukaryotes (protozoa and yeast) have also been referred to as apoptosis. In recent years apoptosis has further been identified in bacteria several times. As a bacterial response to external stimuli, apoptosis could be important not only for the bacteria but also to the host .

What makes a cell decide to commit suicide?

- **Withdrawal of positive signals**

  examples :

  growth factors for neurons

  Interleukin-2 (IL-2)

- **Receipt of negative signals**

  examples :

  increased levels of oxidants within the cell

  damage to DNA by oxidants

  death activators :

  Tumor necrosis factor alpha (TNF-α)

  Lymphotoxin (TNF-β)

  Fas ligand (FasL)

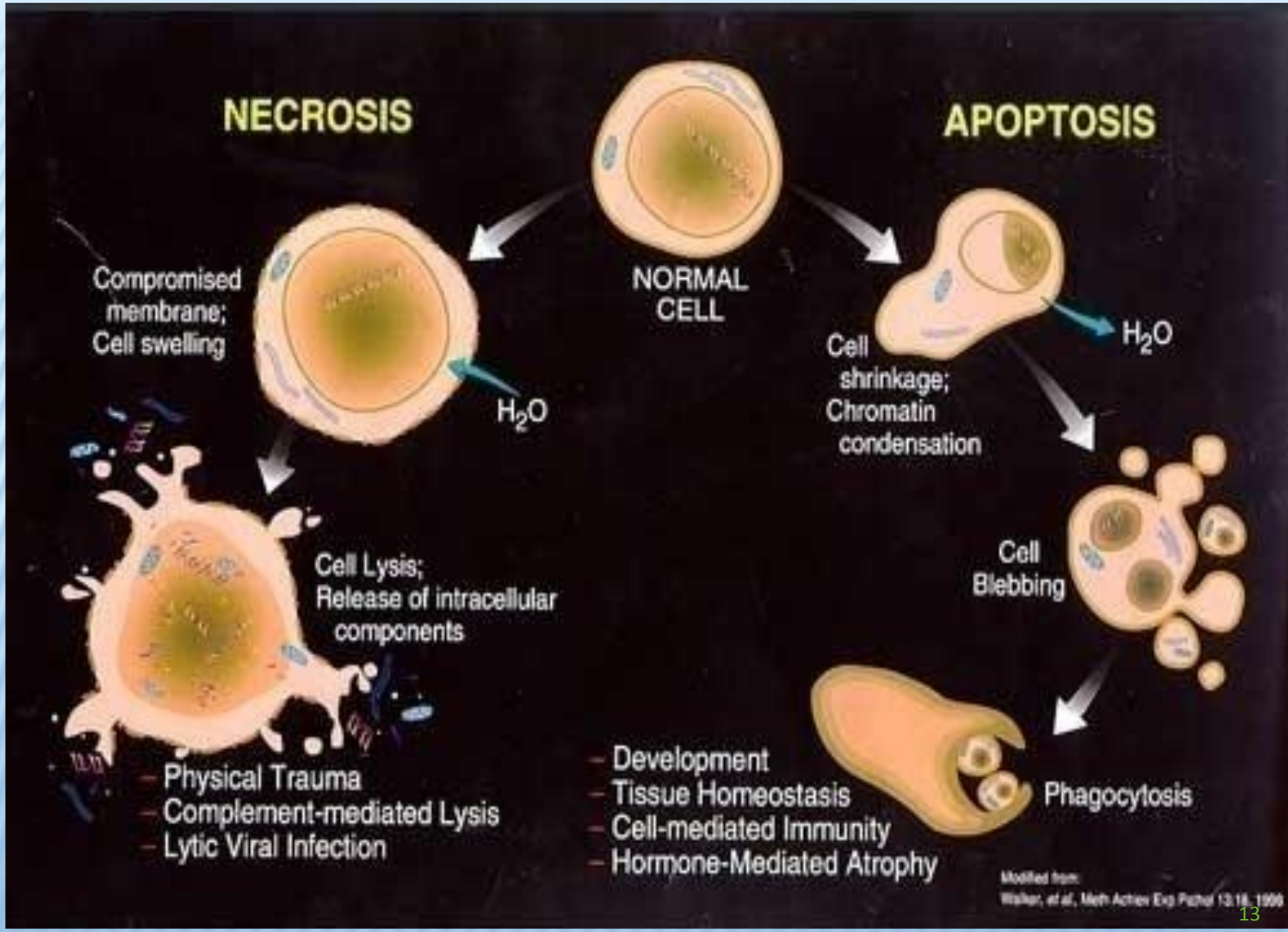
Necrosis *vs.* Apoptosis

Necrosis

- Cellular swelling
- Membranes are broken
- ATP is depleted
- Cell lyses, eliciting an inflammatory reaction
- DNA fragmentation is random, or smeared
- In vivo, whole areas of the tissue are affected

Apoptosis

- Cellular condensation
- Membranes remain intact
- Requires ATP
- Cell is phagocytosed, no tissue reaction
- Ladder-like DNA fragmentation
- In vivo, individual cells appear affected


NECROSIS
APOPTOSIS
NORMAL CELL
Compromised membrane; Cell swelling
H_2O
Cell shrinkage; Chromatin condensation
H_2O
Cell Lysis; Release of intracellular components
Cell Blebbing
– Physical Trauma
– Complement-mediated Lysis
– Lytic Viral Infection
– Development
– Tissue Homeostasis
– Cell-mediated Immunity
– Hormone-Mediated Atrophy
Phagocytosis
Modified from
Walker, et al., Meth Achiev Exp Pathol 13:18, 1988

Apoptosis: Pathways

"Extrinsic Pathway"

Death Ligands

Death Receptors

Initiator Caspase 8

Effector Caspase 3

"Intrinsic Pathway"

DNA damage & p53

Mitochondria/Cytochrome C

Initiator Caspase 9

apoptosis_seq2_apoptosis_440x276.mp4

Bacteria-induced apoptosis

Escherichia coli

The apoptotic episode caused by *E. coli has been* associated mainly with the ability of some *E. coli* (STEC) to produce a Shiga-like toxin, including the most common serotype (O157:H7).

Caspase-8 is involved in the Shiga-like toxin-mediated apoptosis of epithelial cells. However, whether the Shiga-like toxin activates caspase-8 directly via Gb3 binding

or indirectly through death receptors and ligands remains to be elucidated. The activation of caspase-8 probably results in the induction of cytochrome c release from the mitochondria , thereby activating procaspase-3, which in turn activates caspase-9 and the mitochondria death pathway.

Shigella

internalization and subsequent escape into the cytosol are essential for pathogenesis. In the cytosol, *S. flexneri* translocates the plasmid-encoded invasion antigen B (IpaB) via a type-III secretion system. IpaB directly binds and activates caspase-1, and its translocation results in apoptosis The induction of apoptosis by *Shigella is tissue-specific and this bacterium does* not induce apoptosis in epithelial cells.

Salmonella

intracellular *Salmonella secretes an* IpaB homolog (SipB) into the cytosol, where it directl binds to and activates caspase-1

Salmonella enterica

- This pathway prevents cytochrome c release, which inhibits activation of the caspase cascade. Akt phosphorylation and activation during infection occurs due to secretion of a type III secretion system (T3SS) effector, SopB. A DsopB mutant is unable to prevent camptothecin-induced apoptosis

Helicobacter pylori

- **Apoptosis and cell cycle control are processes required for the regulation of cellular homeostasis**
- **chronic imbalance between apoptosis and cell proliferation is the first step of gastric carcinogenesis, as in all tumours.**
- ***H. pylori* infection could lead to an overall increase in cellular turnover and persistence of mutated cells, which will favour the development of neoplasia**

- The *H. pylori* toxin VacA induces gastric epithelial cell apoptosis, suggesting that differences in levels of gastric mucosal apoptosis among infected persons might result from strain-dependent variations in VacA structure.

Neisseria

Muller
et al. demonstrated that the N. gonorrhoeae porin PorB1B interacts with HeLa cell mitochondria and induces calcium efux and apoptosis.

However, meningococcal PorB can protect against mitochondrial apoptosis induced by staurosporine.

Bacterial pathogens have evolved several ways to prevent apoptosis:

1-Protection of the mitochondria and prevention of cytochrome c Release

- Chlamydia and Neisseria

2-Activation of cell survival pathways

- Salmonella, Anaplasma, Ehrlichia, Rickettsia, Wolbachia and Bartonella

3-Interaction with cellular caspases

- Shigella and Legionella

The bacteria that use apoptotic prevent mechanisms

- *Listeria monocytogenes*
- *Mycobacterium tuberculosis*
- *Haemophilus infuenzae*
- *Neisseria meningitides*
- *Neisseria gonorrhoeae*
- *Rickettsia*
- *Chlamydia*

Table 1. Classification of bacteria that inhibit apoptosis

Pathogens grouped by class	Cell type[a]	Proposed or demonstrated mechanism	Refs
Protection of mitochondria			
Chlamydia sp.	Hep2, HeLa	Inhibits and degrades pro-apoptotic proteins	[15–20]
Neisseria sp.	HeLa, UEC	Prevents cytochrome *c* release	[21,22,25–27,2
Activation of cellular pathways			
Salmonella enterica	HeLa, IEC-6	Activates PI3/Akt pathway	[30]
Anaplasma phagocytophilum	Neutrophils	Activates p38 MAPK, ERK, PI3/Akt, NF-κB pathways	[32–34]
Ehrlichia chaffeensis	THP-1	Activates NF-κB and upregulates pro-survival genes	[35]
Rickettsia rickettsii	HUVEC	Prevents cytochrome *c* release	[36,37]
Wolbachia	Neutrophils	Prevents caspase-3 activation	[38,39]
Bartonella sp.	Mono Mac 6, HUVEC	Activates NF-κB pathway, induces *cIAP-1, cIAP-2* expression	[40–42]
Helicobacter pylori	MKN45	Induces *cIAP-2* expression through NF- κB activation	[53]
Porphyromonas gingivalis	GEC	Activates PI3/Akt pathway	[55]
Listeria monocytogenes	J774	Activates PI3/Akt and NF-κB pathways	[56]
Interaction with caspases			
Shigella flexneri	HeLa, T84	Inhibits caspase-3 activation despite cytochrome *c* release	[44]
Legionella pneumophila	U937	Activates NF-κB pathway and upregulates pro-survival genes	[46–48]
Further investigation required			
Mycoplasma fermentans	U937	Inhibits TNFα-induced apoptosis	[57,58]
Brucella suis	THP-1	Upregulates pro-survival genes	[59]
Escherichia coli K1	THP-1, RAW 264.7	Upregulates pro-survival genes	[60]
Coxiella burnetii	HeLa, THP-1	Prevents cytochrome *c* release	[61,62]

chlamydial

The chlamydial proteasome-like activity factor (CPAF), a protease that is secreted by C. trachomatis, was identified as the bacterial product required for the degradation of the pro-apoptotic proteins In addition, Chlamydia could also upregulate the inhibitor of apoptosis proteins (IAPs) when tumor necrosis factor a (TNF-a) was used as an inducer of the extrinsic pathway of apoptosis.

In addition to blocking apoptosis, Chlamydia-infected cells continue to undergo DNA synthesis and mitosis up to 40 h post-infection, which aids in establishing a persistent Infection .Preventing apoptosis would help ensure that the eukaryotic cell continues to divide in the presence of apoptotic signals from the host.

Rickettsia rickettsii

- the obligate intracellular pathogen Rickettsia rickettsii prevents apoptosis in endothelial cells in an NF-kB-dependent manner, which results in the upregulation of pro-survival proteins, the downregulation of pro-apoptotic proteins, and a lack of cytochrome c release and caspase activation.

Bartonella henselae

Bartonella henselae activates NF-kB,
leading to
increased expression of cIAP-1 and cIAP-2
inhibition of caspase-3 activation and
apoptosis .

Mycobacterium Tuberculosis

Apoptosis has been assigned a role in the immune response against Mtb

This is achieved in part by the product of the gene *nuoG*, as deletion of this gene from mycobacteria results in elevated levels of apoptosis.

Inhibition of apoptosis

- Mycobacterial Man-LAM:

  -prevents the Ca++ increase that would increase mitochondrial permeability and cytochrome c release.

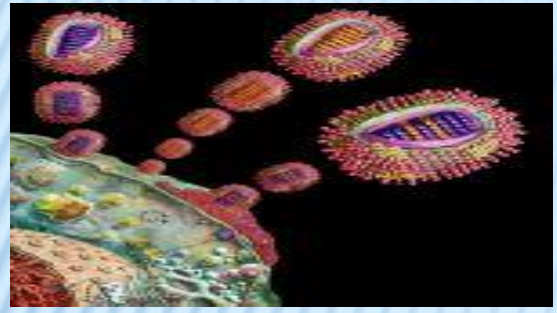
  -activates the Akt cascade that phosphorylates Bad to keep it from binding Bcl-2. Free Bcl-2 inhibits cytochrome c release and inhibits caspase activity.

- IL-10 production:

  - releases TNFR2 to block TNF-α activity that would activate the death receptor and external apoptotic cascade.

Virus & Apoptosis

Viral regulation of apoptosis



Anti-apoptotic regulation?
Pro-apoptotic regulation?

What does mean viral apoptotic regulation?

Survival Viral

Immune system and viral immune escape

Apoptosis related viral proteins

- Influenza virus (Flu)
  → NS, NA, PB1-F2

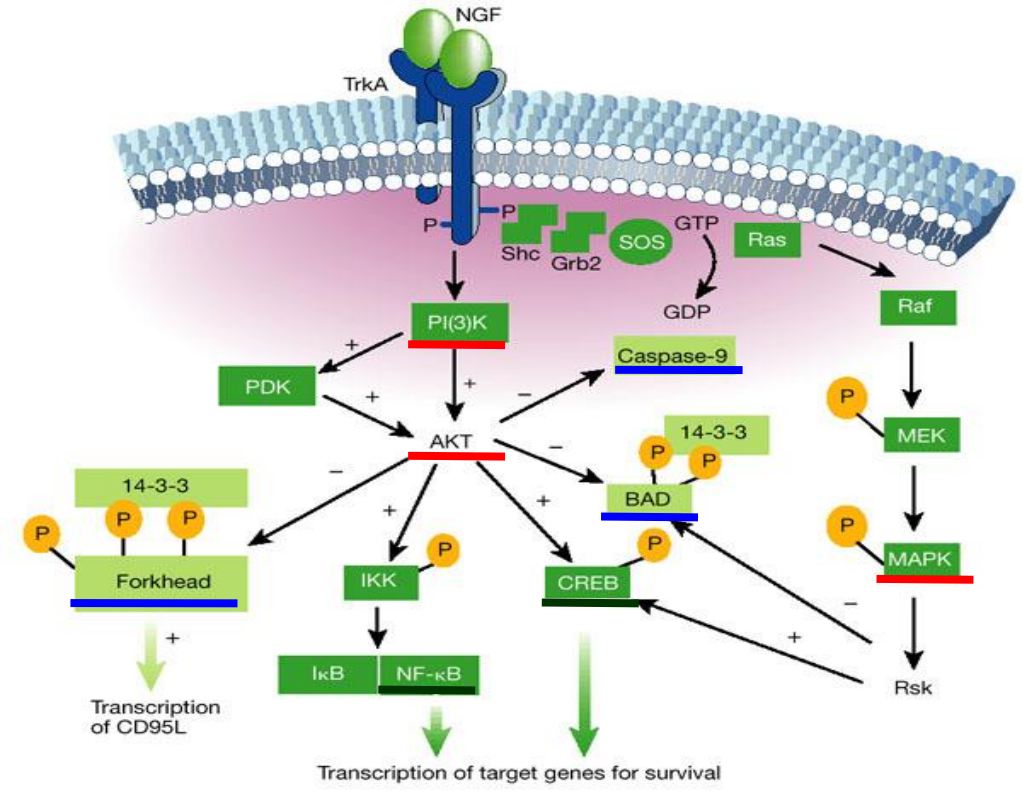
- Hepatitis B virus (HBV)
  → HBx, HBc

- Hepatitis C virus (HCV)
  → NS5A, NS3, NS2, HCV core

- Human immunodeficiency virus (HIV)
  → Tat, Vrp, Nef, Vpu, Env, Protease

- Etc

Survival signals in neuron by trophic factor



- Activation of prosurvival signals : PI3K, AKT, ERK
- Inhibition of prodeath signals: BAD, Forkhead, caspase
- Net outcome: Activating NF-kB and CREB signaling

Inhibition of apoptosis

- Mycobacterial Man-LAM:

  -prevents the Ca++ increase that would increase mitochondrial permeability and cytochrome c release.

  -activates the Akt cascade that phosphorylates Bad to keep it from binding Bcl-2. Free Bcl-2 inhibits cytochrome c release and inhibits caspase activity.

- IL-10 production:

  - releases TNFR2 to block TNF-α activity that would activate the death receptor and external apoptotic cascade.

Viral regulation of apoptosis

Human Immunodeficiency Virus

(H I V)

- Pro-apoptpsis

➢**HIV-1 gp120- and gp160-induced apoptosis in cultured endothelial cells is mediated by caspases**

➢**HIV-1 Tat targets microtubules to induce apoptosis, a process promoted by the pro-apoptotic Bcl-2 relative Bim**

➢**HIV-1 Vpr is expressed in brains of HIV-1-infected patients and induces neuronal cell death.**
HIV-1 Vpr induces the intrinsic apoptosis pathway in neuronal cells

➢HIV-1 protease is present in the cytosols of infected cells and cleaves procaspase 8 into a novel p41 fragment. Casp8p41 induces apoptosis.

Anti-apoptpsis

- **HIV-1 Nef associated PAK and PI3-Kinases stimulate Akt-independent Bad-phosphorylation to induce anti-apoptotic signals**

- **Vpu : Downregulation of CD4 receptor on infected cell**
- Tat : **Cell-cycle progression by decreasing TP53 transcription**

Influenza Virus

- **A novel influenza A virus mitochondrial protein that induces cell death.**
  - **Influenza PB1-F2 localized in the mitochondria of infected cells**

Hepatitis B Virus
(H B V)

- **The Hepatitis B Virus-X Protein Activates a Phosphatidylinositol 3-Kinase-dependent Survival Signaling Cascade**

Hepatitis C Virus
(H C V)

- NS5A(SH3 binding motif) Binds to Bin1(SH3 domain) In Vitro and In Vivo
- Colocalization of HCV NS5A and Bin1 by confocal microscopy

- Effects of NS5A and Bin1 expression on apoptosis of cells.

- Identification of the NS2-binding domain in the human CIDE-B protein.
  NS2 associates with CIDE-B in the cell.

- **The Hepatitis C Virus NS2 Protein Is an Inhibitor of CIDE-B-induced Apoptosis***

HSV-1

- LAT inhibits apoptosis by a Dicer dependent mechanism.
- The LAT gene of codes for a miRNA.
- The LAT region of HSV-1 17*1* protects cells from apoptosis.

Anti-apoptotic function of a microRNA encoded by the HSV-1 latency-associated transcript

HSV

The US3 protein kinase of HSV- 1 mediates the post translational modification of BAD and prevents BAD-induced programmed cell death in the absence of other viral proteins

Coxsackievirus

- **Coxsackievirus Protein 2BC Blocks Host Cell Apoptosis by Inhibiting Caspase-3**

Reovirus

- Reovirus-induced apoptosis requires both death receptorand mitochondrial-mediated caspase-dependent pathways of cell death

Vaccinia Virus

- The Vaccinia Virus Protein F1L Interacts with Bim and Inhibits
  Activation of the Pro-apoptotic Protein Bax*

Institut Pasteur
Microbes and Infection 15 (2013) 640–644

Commentary

Is there, and should there be, apoptosis in bacteria?

Abstract

Apoptosis is a well-studied form of cell death in metazoans, where it has a clear role during the life of the (multicellular) animal. Some situations of cell death in unicellular eukaryotes (protozoa and yeast) have also been referred to as apoptosis. In recent years apoptosis ha further been identified in bacteria several times. As a bacterial response to external stimuli, apoptosis could be important not only for the bacte but also to the host. Here I will discuss why I believe that the term apoptosis should be avoided for these situations in bacteria, no matter h teresting the molecular background or how biologically important the underlying mechanism may be.

Apoptosis; Necrosis; Bacteria; Evolution

can be expl

MINI-REVIEW

CTERIA-INDUCED APOPTOSIS: AN APPROACH TO BACTERIAL PATHOGENESIS

Marcelo Lancellotti, Marcelo Brocchi, Wanderley Dias da Silveira

oratory of Bacterial Molecular Biology, Department of Microbiology and Immunology, Institute of Biology, State University of Campinas (UNICAMP), Campinas, SP, Brazil.

CT

opportunistic bacteria can induce or inhibit host cell apoptosis. T induction or delay of host cell apop

Review

Cell PRESS

Staying alive: bacterial inhibition of apoptosis during infection

Christina S. Faherty and Anthony T. Maurelli

Department of Microbiology and Immunology, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814-4799, USA

The ability of bacterial pathogens to inhibit apoptosis in eukaryotic cells during infection is an emerging theme in the study of bacterial pathogenesis. Prevention of apoptosis provides a survival advantage because it enables the bacteria to replicate inside host cells. Bacterial pathogens have evolved several ways to prevent apop

Figure 2), we review the various ways that bacterial pathogens inhibit apoptosis. Bacterial pathogens can be grouped into three classes based on the mechanisms employed to inhibit apoptosis. Here, we describe these three mechanisms and provid


Thank
You!!